Table 1: Subject Characteristics

	Healthy	Asthma
Induced sputum study		
n	11	35
Age, yr	37 ± 12	36 ± 13
Female, n (%)	5 (45)	23 (66)
BMI, kg/m^2	26.6 ± 4.9	28.7 ± 7.1
FEV_1, L	4.01 ± 1.00	2.73 ± 0.90
FEV_1, % predicted	108.1 ± 11.0	79.1 ± 17.4
PC_{20} (n = 31)	N/A	0.69 (0.12–12.60)
On ICS, n (%)	N/A	19 (54)
Smoking history		
Never, n (%)	8 (73)	17 (49)
Former, n (%)	3 (27)	18 (51)
Pack-years	0 (0–1.36)	0 (0–10.00)
Acute asthma study		
n		11
Age, yr		43 ± 11
Female, n (%)		8 (73)
On ICS, n (%)		9 (82)
On LABA, n (%)		6 (55)
On anticholinergic, n (%)		3 (27)
% admitted		2 (18)
Smoking history		
Never, n (%)		3 (27)
Former, n (%)		7 (64)
Current, n (%)		1 (9)
Pack-years		1 (0–8)
On ICS, n (%)		3 (60)
Mucin study		
n		5
Age, yr		39.4 ± 14.5
Female, n (%)		3 (60)
BMI, kg/m^2		29.7 ± 7.4
FEV_1, L		2.55 ± 0.86
FEV_1, % predicted		73.6 ± 17.4
Smoking history		
Never, n (%)		3 (60)
Former, n (%)		2 (40)
Pack-years		0 (0–8.5)
PC_{20}		0.39 (0.15–1.19)
On ICS, n (%)		3 (60)

Definition of abbreviations: BMI = body mass index; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; PC_{20} = provocative concentration of methacholine (mg/ml) that results in a 20% fall in FEV_1. Values are presented as mean ± SD or median (range), unless otherwise noted.

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Antioxidants in the Intensive Care Unit

To the Editor:

The Critical Care Perspective review of the use of antioxidants in the intensive care unit (ICU) by Jain and Chandel in the December 1, 2013, issue of the *Journal* (1) presented a possible mechanism for the lack of a positive outcome in most clinical trials using these agents. However, understanding possible approaches for the prevention of acute oxidant stress in the ICU requires taking the kinetics of the various redox-related reactions into consideration. In essence, effectiveness of an antioxidant requires it to outcompete the interaction of the oxidant with tissue components, for it is the latter interaction that results in tissue injury. It is not

known precisely which of the reactive oxygen species (ROS) are responsible for the bulk of tissue injury, and that may vary depending on the inciting agent and other circumstances. One important reaction may be the interaction of ferrous iron (Fe^{2+}) with H_2O_2 to generate hydroxyl radical ($^{\bullet}OH$) (Fenton reaction). Both the generation of $^{\bullet}OH$ by this reaction and its subsequent interaction with tissue components are essentially instantaneous, and there is no conceivable way for a potential scavenger compound to out-compete those reactions. Superoxide dismutase will not prevent tissue oxidation under these conditions, but rather, if the rate of superoxide production is rate limiting, will increase the H_2O_2 flux that is the source of $^{\bullet}OH$ radicals. ROS generated by other reactions may be more susceptible to the action of antioxidants, but only at the expense of some tissue damage. As such, it is understandable, as concluded by Jain and Chandel, that antioxidants may not be effective in the treatment of acute lung injury associated with oxidant stress (1). However, there may be some hope; that is, preventing the generation of ROS could be an effective strategy to prevent lung injury. Jain and Chandel indicated that a major source of ROS with acute lung injury is through activation of one or more of the reduced nicotinamide adenine dinucleotide (NADPH) oxidases (1). There has recently been considerable research activity related to the development of nontoxic inhibitors of NADPH oxidases (2, 3), including one from our laboratory based on inhibiting the activation pathway for NADPH oxidase type 2 (4–6). It seems likely that potential therapeutic agents based on inhibition of this group of enzymes will be developed for use in the ICU in the near future. Thus, it is premature to abandon hope for preventing oxidant-induced lung injury in the intensive care setting. ■

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Reply

From the Authors:

We thank Drs. Fisher and Forman for their thoughtful description of the detrimental effects of high levels of reactive oxygen species (ROS), which we agree are likely to contribute to tissue injury during disease through Fenton chemistry and other reactions. In our perspective (1), we highlight the recent paradigm shift in oxidant biology, which recognizes that low levels of ROS serve as signaling molecules that play key roles in the biologic adaptation to environmental stress and pathogen challenge. We suggest that the unrecognized interruption of these pathways might explain why the current arsenal of nonselective antioxidants, including *N*-acetylcysteine, vitamin C, and vitamin E, have failed in clinical trials in the intensive care unit and in other disease models, and we suggest that trials of these and other nonselective antioxidants should no longer be pursued. We agree that selectively targeted antioxidants—for example, those designed to specifically target the NADPH oxidase or mitochondrial ROS generation—continue to hold promise; however, we suggest that their use must be coupled with a clear understanding of their normal biologic function. For example, NADPH oxidases play an important role in pathogen clearance, vascular reactivity, and lung repair. Whether the cost of inhibiting these normal, oxidant-dependent signaling pathways is justified by the benefit of preventing oxidant-mediated tissue injury is not immediately clear. ■

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Classification of the Idiopathic Interstitial Pneumonias

To the Editor:

The recently revised American Thoracic Society/European Respiratory Society classification of the idiopathic interstitial